Chemistry of Heterocyclic Compounds, Vol. 32, No. 3, 1996

SYNTHESIS OF ADENINE DERIVATIVES CONTAINING AN AMINO ALCOHOL FRAGMENT

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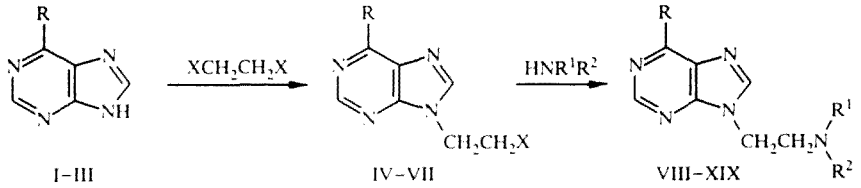
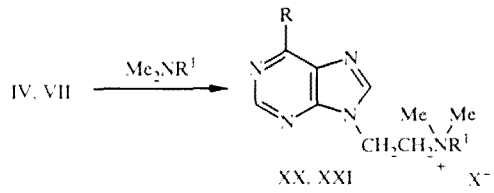
The alkylation of adenine and $N_{(6)}$-substituted adenine derivatives by 1,2-dihaloethanes and the production of 9-(2-haloethyl)derivatives of adenine were studied. In the reaction of the derivatives with amino alcohols a series of adenine derivatives containing an amino alcohol fragment was synthesized.

Continuing our investigations on the synthesis of purine derivatives [1-4], we synthesized a series of adenine derivatives containing an amino alcohol group in the acyclic chain. The interest in such compounds is due to the diverse biological activity (antiviral, antitumor, etc.) that is possessed by natural azacarbohydrate alkaloids [5, 6].



I, IV, VIII—XII R = NH_2; II, V, XIII—XV R = NMe_2; III, VI, VII, XVI—XIX R = $N(C_2H_5)_2$; VIII—XI, XIII—XVIII R^1 = H; XII R^1 = $CH_2C_6H_5$; XIX R^1 = —CH_2CH_2OH; VIII, XII, XIII, XVI, XIX R^2 = CH_2CH_2OH; IX, XIV, XVII R^2 = $CH_2CH(OH)CH_3$; X, XV, XVIII R^2 = $CH(CH_2OH)_2$; XI R^2 = $C(CH_2OH)_3$; X = Cl, Br



XX R = NH_2, R^1 = CH_2CH_2OH, X = Cl; XXI R = NEt_2, R^1 = $CH_2CH(OH)CH_3$, X = Br

9-(2-Chloro(bromo)ethyl derivatives of adenine IV-VII were obtained with yields of 54-76% by alkylation of the corresponding purine compounds I-III with 1,2-dichloroethane, 1-bromo-2-chloroethane, or 1,2-dibromoethane in the systems: benzene—50% aqueous NaOH—0.1 equivalent of tetrabutylammonium bromide (for V-VII) and benzene—solid KOH—0.1 equivalent of trioctylmethylammonium chloride (for IV). The method used significantly surpasses the method used previously for the synthesis of 9-(2-chloroethyl)adenine (IV) (sodium hydride—DMFA) [7] in yield and simplicity.

The structure of the intermediates IV-VII obtained was demonstrated by comparing the data of PMR and UV spectroscopy with the data that were obtained earlier in an investigation of the alkylation of purine derivatives [1-4, 8, 9]. The physicochemical characteristics of 9-(2-haloethyl)derivatives of adenine IV-VII are presented in Tables 2 and 3.

Latvian Institute of Organic Synthesis, Riga LV-1006. Translated from Khimiya Geterotsiklicheskikh Soedinenii, No. 3, pp. 386-390, March, 1996. Original article submitted March 7, 1995.

0009-3122/96/3203-0333$15.00

TABLE 1. Conditions of Synthesis of Adenine Derivatives VIII-XXII*

Compound	Initial	Amino alcohol** (3 moles/eq.)	Solvent, ml/mmole (butanol)	Reaction time, h	Yield % (solvent for crystallization)
VIII †	IV	A	0,4	2	62 (EtOH)
IX †	IV	B	0,5	5	56 (EtOH)
X	IV	C	0,4	5	67 (EtOH)
XI	IV	D	0,5	15	71 (EtOH)
XII ‡	IV	E	0,5	5	53 (EtOH)
XIII †	V	A	1,1	3	38 (Ether)
XIV †	V	B	1,1	5	43 (Ether)
XV †	V	C	1,1	10	32 (Isopropanol)
XVI †	VI	A	0,5	3	41 (Ether)
XVII †	VI	B	0,5	5	34 (Ether)
XVIII ‡	VI	C	0,5	10	48 (Ether)
XIX ‡	VI	F	0,5	5	55 (Acetonitrile)
XX	IV	G	0,5	10	73 (Acetonitrile)
XXI	VI	H	0,5	10	38 (Ether)

*Temperature 110°C; for VIII and X, 100°C.

†Hydrochloride.

‡Dihydrochloride.

**A) aminoethanol; B) 1-aminoisopropanol; C) 2-aminopropanediol-1,3; D) tris(hydroxymethyl)aminomethane; E) 2-benzylaminoethanol; F) diethanolamine; G) 2-dimethylaminoethanol; H) 1-dimethylaminoisopropanol.

TABLE 2. Physicochemical Characteristics of Derivatives V-XXI

Compound	UV spectrum, λ_{max}, nm (methanol)	mp, °C	Gross formula	Mol. mass
V	280	117...118	$C_9H_{12}ClN_5$	225,5
VI	280	56...58	$C_{11}H_{16}ClN_5$	253,5
VII	280	70...72	$C_{11}H_{16}BrN_5$	298,3
VIII	258*	235...236	$C_9H_{14}N_6O \cdot HCl$	259,6
IX	258*	223...224	$C_{10}H_{16}N_6O \cdot HCl$	272,7
X	258*	162...163	$C_{10}H_{16}N_6O_2$	252,2
XI	258*	190...191	$C_{11}H_{18}N_6O_3$	282,1
XII	258*	220...222	$C_{16}H_{20}N_6O \cdot 2HCl \cdot 2H_2O$	421,3
XIII	280	244...245	$C_{11}H_{18}N_6O \cdot HCl$	286,5
XIV	280	222...223	$C_{12}H_{20}N_6O \cdot HCl$	300,6
XV	268†	104...105 (dec.)	$C_{12}H_{20}N_6O_2 \cdot HCl \cdot H_2O$	333,5
XVI	280	195...196	$C_{13}H_{22}N_6O \cdot HCl$	315,2
XVII	280	205...206	$C_{14}H_{24}N_6O \cdot HCl$	328,6
XVIII	280	142...143 (dec.)	$C_{14}H_{24}N_6O_2 \cdot 2HCl$	361,5
XIX	268†	157...158 (dec.)	$C_{15}H_{26}N_6O_2 \cdot 2HCl \cdot 1/2\ H_2O$	404,1
XX	258*	230...231 (dec.)	$C_{11}H_{19}ClN_6O$	285,8
XXI	280	168...169	$C_{16}H_{29}BrN_6O$	401,1

*Water, pH 1.

†Water, pH 7.

The target derivatives of adenine VIII-XXI were synthesized by heating the intermediates IV-VII with the corresponding amino alcohol in butanol. The reaction proceeds almost quantitatively; the yields of the derivatives VIII-XXI depend chiefly on the losses during their crystallization.

TABLE 3. Data of PMR Spectra of Adenine Derivatives V-XXI

Compound	Chemical shift, δ, ppm (DMSO-D_6)
V*	4,55 (6H, s, CH_3), 4,93 (2H, t, CH_2), 5,53 (2H, t, CH_2), 8,80 (s), 9,35 (2H, s, Purine 4)
VI*	1,26 (6H, t, CH_3), 3,98 (6H, m, NCH_2), 4,51 (2H, t, CH_2), 7,84 (s), 8,35 (2H, s, Purine 4)
VII*	1,29 (6H, t, CH_3), 3,62...4,04 (6H, m, NCH_2), 4,56 (2H, t, CH_2), 7,78 (s), 8,29 (2H, s, Purine 4)
VIII	3,02 (2H, t, CH_2), 3,46 (2H, t, CH_2), 3,66 (2H, br.s, CH_2), 4,53 (2H, t, CH_2), 5,24 (1H, br.s, OH), 7,28 (2H, br.s, NH_2), 8,15 (2H, s, Purine 4)
IX	1,11 (3H, d, CH_3), 3,44 (4H, m, CH_2), 3,77...4,13 (1H, m, CH), 4,53 (2H, t, CH_2), 5,36 (1H, d, OH), 7,27 (2H, br.s, NH_2), 8,13 (2H, s, Purine 4)
X	2,95 (2H, t, CH_2), 3,28 (7H, br.s, CH_2, CH), 4,33 (2H, br.s, OH), 7,09 (2H, br.s, NH_2), 8,09 (2H, s, Purine 4)
XI	3,00 (2H, t, CH_2), 3,40 (2H, s, CH_2), 3,80...4,91 (10H, m, CH_2, OH, NH), 6,31 (2H, br.s, NH_2), 8,09 (s), 8,12 (2H, s, Purine 4)
XII	3,20 (2H, m, CH_2O), 3,51...3,91 (4H, m, NCH_2), 4,44 (2H, s, CH_2Ph), 4,80 (2H, t, N_9CH_2), 5,68...7,15 (3H, br.s, $OH+H_2O$), 7,37 (5H, m, Ph), 7,60 (2H, br.s, CH_2), 8,49 (s), 8,60 (2H, s, Purine 4), 8,71...9,82 (2H, br.s, HCl)
XIII	3,04 (2H, m, CH_2), 3,38...3,78 (10H, m, $2CH_2$, $2CH_3$), 4,53 (2H, t, CH_2), 5,29 (1H, t, OH), 8,13 (s), 8,22 (2H, s, Purine 4), 9,15 (2H, br.s, NH×HCl)
XIV	1,11 (3H, d, CH_3), 2,65...3,11 (3H, m, CH_2CH), 3,44 (6H, s, $2CH_3$), 3,93 (2H, br.s, CH_2), 4,55 (2H, t, CH_2), 5,37 (1H, d, OH), 8,13 (s), 8,18 (2H, s, Purine 4)
XV	3,44 (6H, s, CH_3), 3,49...3,62 (7H, m, CH_2, CH), 4,51 (2H, t, CH_2), 5,29 (2H, t, OH), 8,06 (s), 8,17 (2H, s, Purine 4), 8,95 (2H, br.s, NH·HCl)
XVI	1,22 (6H, t, CH_3), 3,02 (2H, m, CH_2), 3,30...4,11 (8H, m, CH_2), 4,51 (2H, m, CH_2), 5,26 (1H, m, OH), 8,12 (2H, s, Purine 4), 9,22 (2H, br.s, NH·HCl)
XVII	1,21 (9H, m, CH_3), 3,02 (2H, m, CH_2), 3,30...3,60 (6H, m, CH_2), 3,93 (3H, br. s, CH_3), 4,51 (2H, m, CH_2), 5,37 (1H, m, OH), 8,11 (s), 8,20 (2H, s, Purine 4)
XVIII	1,21 (6H, t, CH_3), 3,55 (8H, t, CH_2), 3,88 (5H, br.s, CH_2CH), 4,51 (2H, m, CH_2), 5,26 (2H, m, OH), 8,08 (s), 8,16 (2H, s, Purine 4), 9,10 (2H, br.s, NH·HCl)
XIX	1,22 (6H, t, CH_3), 3,31 (4H, br.s, CH_2O), 3,55...4,33 (1H, m, NCH_2), 4,71 (2H, t, N_9CH_2), 6,33...7,66 (3H, m, OH+HCl), 8,33 (s), 8,47 (2H, s, Purine 4), 10,42 (1H, br.s, HCl)
XX	3,15 (6H, s, CH_3), 3,44...3,66 (2H, m, CH_2O), 3,68...4,06 (4H, m, CH_2N), 4,71 (2H, t, N_9CH_2), 5,58 (1H, t, OH), 7,24 (2H, s, NH_2), 8,16 (s), 8,27 (2H, s, Purine 4)
XXI	1,16 (9H, m, CH_3), 3,04...3,60 (10H, m, $N+CH_2$, N^+CH_3), 3,93 (6H, m, NCH_2), 4,27 (1H, m, CH), 4,71 (2H, t, N_9CH_2), 5,38 (1H, d, OH), 8,22 (s), 8,31 (2H, s, Purine 4)

*The spectrum was taken in $CDCl_3$.

The conditions of synthesis and method of isolation of the adenine derivatives VIII-XXI are presented in Table 1, and the physicochemical characteristics in Tables 2 and 3. The FAB mass spectra of the adenine derivatives VIII-XXI contained distinct peaks ($M+H^+$) in all cases.

EXPERIMENTAL

The ^1H PMR spectra were recorded on a Bruker WH-90 spectrometer; the chemical shifts were measured relative to an internal standard TMS. The UV spectra were recorded on a Specord spectrophotometer, the FAB mass spectra on an MS-50 spectrometer, using an FAB 11 ion source (Ion Tech., Ltd.).

Analytical thin-layer chromatography was conducted on plates of Silufol UV-254 in the systems chloroform—ethyl acetate, 1:1 (A) and chloroform—methanol, 8:2 (B) (volume ratios). Column chromatography was conducted on columns (2 × 30 cm) (system A) and (4 × 4 cm) (system B) with silica gel L 40/100.

9-(2-Chloroethyl)adenine (IV). A mixture of 2.71 g (20 mmoles) of adenine I, 1.23 g (22 mmoles) of finely pulverized KOH, 0.8 g (2 mmoles) of Aliquat 336, and 8 ml of benzene was heated for 1 h at 80°C. Then 20 ml of 1,2-dichloroethane was added, and the mixture was mixed for 5 h at 80°C. The reaction mixture was cooled, filtered, and washed with benzene. The solid residue was extracted twice with hot chloroform. The extract was evaporated, and the dry residue was crystallized from water. Yield of compound IV 1.62 g (41%). Mp 201-202°C. The data of the UV and PMR spectra of a sample of the product IV, recrystallized from ethanol, agree with the literature data [7].

TABLE 4. Data of Elementary Analysis of Adenine Derivatives V-XXI

Compound	Found, % / calculated, %		
	C	H	N
V	47.85 47.89	5.30 5.30	30.94 31.04
VI	52.03 52.11	6.31 6.31	27.54 27.61
VII	44.32 44.60	5.37 5.35	23.50 23.34
VIII	41.14 41.40	5.98 5.98	32.85 32.45
IX	44.30 44.04	6.33 6.23	30.83 30.80
X	47.25 47.58	6.23 6.34	33.36 33.30
XI	46.62 46.83	6.41 6.38	29.43 29.78
XII	45.68 45.61	5.86 6.22	19.97 19.94
XIII	46.13 46.07	6.59 6.63	29.35 29.32
XIV	47.64 47.84	7.00 6.99	27.23 27.84
XV	42.91 43.20	6.95 6.90	24.92 25.18
XVI	49.94 49.60	7.22 7.21	26.84 26.71
XVII	50.83 51.04	7.72 7.61	25.47 25.57
XVIII	46.75 46.50	7.61 7.47	23.62 23.24
XIX	44.61 44.63	7.05 7.15	20.63 20.80
XX	46.35 46.23	6.67 6.70	29.18 29.41
XXI	48.07 47.92	7.54 7.23	21.17 20.94

$N_{(6)}$,$N_{(6)}$-Disubstituted 9-(2-Haloethyl)adenines (V-VII). To a suspension of 10 mmoles $N_{(6)}$,$N_{(6)}$-dimethyl-(diethyl)adenine (II, III) in 40 ml of benzene, containing 0.32 g (1 mmole) tetrabutylammonium bromide, we added 25 ml of a 50% aqueous solution of NaOH and 14.3 g (100 mmoles) of 1-chloro-2-bromoethane or 18.8 g (100 mmoles) of 1,2-dibromoethane with mixing. The reaction mixture was mixed at 80°C until the suspension of the sodium salt of the purine disappeared (~ 0.5 h); the mixture was cooled, and 150 ml of water and 100 ml of chloroform were added. The organic layer was removed, and the aqueous layer was washed with chloroform. The combined extracts were dried over Na_2SO_4, evaporated, and chromatographed on silica gel (system A). After chromatography, the products V-VII were washed by crystallization from ether. Yield of V 1.71 g (76%), VI 1.57 g (62%), and VII 1.61 G (54%). The physicochemical characteristics of the adenine derivatives V-VII are given in Tables 2 and 3.

Adenine Derivatives VIII-XXI. The adenine derivatives VIII-XXI were synthesized by heating 9-(2-haloethyl)adenines IV-VII with the corresponding amino alcohols in butanol (Table 1). The reaction mixtures were treated as follows:

a) for compounds VIII-XII: the mixture was diluted with ethanol, left overnight in a refrigerator, filtered, washed with ethanol, and crystallized;

b) for compounds XII-XIX: the mixture was evaporated, chromatographed on a column with silica gel (4 × 4 cm, system B), and crystallized (compounds XII, XVIII, and XIX were converted to the hydrochlorides before crystallization);

c) compounds XX and XXI were precipitated with ether, then crystallized.

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